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The Enantioselective Total Synthesis of Natural (-)-Aphanorphine

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(-)-Aphanorphine, a novel 3-benzazepine alkaloid isolated from the freshwater blue-green alga Aphanizomenon flos-aquae, has been synthesized in an enantioselective fashion.

(-)-Aphanorphine¹ (1), isolated from the freshwater bluegreen alga *Aphanizomenon flos-aquae*, possesses an interesting 3-benzazepine framework related to the natural narcotic alkaloid morphine and the synthetic analgesic pentazocine.² The relative stereochemistry of (1) was deduced spectroscopically and recently its absolute stereochemistry was determined unambiguously by the present authors³ as (1R,4R) by synthesis of the (1S,4S)-antipode (ent-1) starting from (S)-Obenzylglycidol. We report herein the enantioselective total synthesis of natural (1R, 4R)-aphanorphine (1) starting from the known optically active dienone (2) whose asymmetric





Scheme 1. Reagents and conditions:, i, 3-methoxyphenylmagnesium bromide (3.4 equiv.), CuBr·SMe₂ (10%), Me₃SiCl (TMSCl) (2.0 equiv.), hexamethylphosphoramide (HMPA) (2.2 equiv.), -70 °C to room temp., 2 h; ii, o-dichlorobenzene, 12 h, reflux; iii, 30% H₂O₂ (3.0 equiv.), NaOH (0.5 equiv.), MeOH, 0 °C to room temp., 2 h; iv, NH₂NH₂·HCl (3.0 equiv.), NEt₃ (4.5 equiv.), MeCN, 0 °C to room temp., 5 h; v, pyridinium chlorochromate (PCC), CH₂Cl₂, room temp., 4 h; vi, H₂, 10% Pd/C, EtOH, room temp., 8 h; vii, trimethylene dithiotosylate (2.0 equiv.), Bu^tOK (3.0 equiv.), tetrahydrofuran (THF), Bu^tOH, 0 °C; viii, KOH (4.0 equiv.), Bu^tOH, 60 °C, 12 h; ix, CH₂N₂, Et₂O; x, *m*-chlorobenzoic acid (MCPBA) (1.0 equiv.), NaHCO₃ (3.0 equiv.), -30 °C, 10 min; xi, TFAA (3.0 equiv.), toluene, 130 °C, 5 min.

synthesis from racemic cyclopentadiene dimer has already been established. 4,5

Treatment of (+)-dienone (2) with 3-methoxyphenylmagnesium bromide in the presence of copper(1) bromide and trimethylsilyl chloride⁶ gave the single 1,4-adduct (3) which, on thermolysis in *o*-dichlorobenzene,^{4,5} afforded the enone (4)† { $[\alpha]_D^{29} + 105.2^\circ (c \ 1.38, CHCl_3)$ } in 87% overall yield by retrograde Diels–Alder reaction. Conversion of (4) to the isomeric enone (7) was carried out by using the Wharton reaction.⁷ Thus, epoxide (5) obtained from (4) as a mixture of diastereoisomers was treated with hydrazine monohydrochloride in acetonitrile⁷ to give the allyl alcohol (6) which was then oxidized to (7) in 62% overall yield. After hydrogenation, ketone (8) { $[\alpha]_D^{27}$ + 83.2° (c 1.21, CHCl₃)} was transformed into the α -diketone monothioketal^{8,9} (9) {[α]_D²⁶ $+39.5^{\circ}$ (c 0.59, CHCl₃) in 53% yield by treatment with trimethylene dithiotosylate¹⁰ and potassium t-butoxide. When (9) was treated with potassium hydroxide in hot Bu^tOH facile ring cleavage¹¹ occurred to afford the acid (10) which gave the ester (11) {[α]_D²⁸ - 19.6° (*c* 1.20 CHCl₃)} in 79% overall yield on exposure to diazomethane. The monosulphoxide (12), obtained quantitatively as a mixture of diastereoisomers from (11) with *m*-chloroperbenzoic acid, underwent facile cyclization to furnish the dihydronaphthalene (17) { $[\alpha]_D^{27} - 70^\circ$ (c 0.97, CHCl₃) in 55% yield as a single regioisomer upon brief treatment with trifluoroacetic anhydride (TFAA) in refluxing toluene (2 min).^{3,12} We believe that the reaction proceeded through the involvement of the transient intermediates such as (13), (14), and (15) with removal of 1,2-dithiolane though we did not detect the latter compound. The ester (17) was

[†] Satisfactory analytical (combustion and/or high resolution mass) and spectral (IR, ¹H NMR, MS) data were obtained for all new isolable compounds.



Scheme 2. Reagents and conditions: i, LiAlH₄, THF, room temp., 20 min; ii, phthalimide (2.0 equiv.), Ph₃P (2.0 equiv.), $(Pr^iO_2CN)_2$ (2.0 equiv.), THF, room temp., 12 h; iii, NH₂NH₂·H₂O (3.0 equiv.), EtOH, reflux, 1 h; iv, Pb(OAc)₄ (1.6 equiv.), K₂CO₃ (6.2 equiv.), benzene, 60 °C to reflux, 20 min; v, FSO₃Me (1.0 equiv.), CH₂Cl₂, 0 °C, 5 min; vi, LiAlH₄, THF, room temp., 30 min; vii, BBr₃, CH₂Cl₂, -30 to 0 °C, 1 h.

reduced to the alcohol‡ (18) whose primary hydroxy group was replaced by a primary amino group by the Mitsunobu reaction¹³ which provided the primary amine (20) *via* the imide (19) { $[\alpha]_D^{27}$ +61.1° (*c* 0.84, CHCl₃)} in 68% overall yield. Upon executing a Nagata reaction,¹⁴ (20) yielded aziridine (21) as an unstable oil which was immediately exposed to methyl fluorosulphonate to give the ammonium salt (22). Treatment of (22) with lithium aluminium hydride allowed selective cleavage at the benzylic σ-bond to afford the penultimate intermediate (23) { $[\alpha]_D^{29}$ +8.46° (*c* 0.915, CHCl₃)} in 24% overall yield from (20). Finally, (23) was treated with boron tribromide to give (–)-aphanorphine§ (1)

[‡] Optical purity of (18) was determined to be >98% enantiomeric excess (e.e.) by ¹H NMR (500 MHz) measurement of its methoxy(tri-fluoromethyl)phenylacetyl (MTPA) (R)- and (S)-ester. Optical purity of synthetic (-)-aphanorphine (1) was determined to be 99.1% e.e. by using a chiral HPLC column (Chiral Selector) which was kindly carried out by Dr. A. Ichida, Daicel Chemical Industries.

{m.p. 215—222 °C (lit.:¹ m.p. 223—229 °C), $[\alpha]_D^{22}$ -46.3° (*c* 0.22, HCl salt in H₂O) [lit.:¹ $[\alpha]_D^{25}$ -43.7° (*c* 0.47, HCl salt in H₂O)]} in 65% yield.

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§ Identical with natural product (TLC, IR, and ¹H NMR spectra) kindly provided by Professor Y. Shimizu.